REMARKS

The Present Invention and Pending Claims

Claims 28-34, 37-40, 43-51, 54, and 56-58 are pending and are directed to a method of creating a transgenic non-human animal containing a gene encoding an expressible dominant negative protein to a naturally occurring cellular protein (claims 28-34, 37, and 57), a transgenic non-human mammal (claims 38-40, 43-51, 56, and 58), and a method of producing a transgenic non-human mammal capable of expressing a protein which has a biological activity of an acidic dominant negative to a cellular protein (claim 54).

Amendments to the Claims

Claim 28 has been amended to recite "embryonic cell" as supported by the specification at, for example, pages 66-66, paragraph [0159]. Claims 35, 36, 41, 42, 52, 53, and 55 have been cancelled as being directed to non-elected subject matter in response to the restriction requirement. Similarly, claims 28, 34, 37, 40, 51, and 54 have been amended to remove non-elected subject matter in response to the restriction requirement. Applicants reserve the right to pursue any canceled subject matter in a continuation, continuation-in-part, divisional application, or other application. Cancellation of any subject matter should not be construed as abandonment of that subject matter. Claims 57 and 58 are new and are supported by the specification at, for example, page 18, paragraph [0051]; page 21, paragraph [0061]; and page 36, paragraph [0088]. Accordingly, no new matter has been added by way of these amendments.

Summary of the Office Action

The Office has made the restriction requirement final. The Office objects to claims 34, 37, 40, 51, 54, and 56 as allegedly containing non-elected embodiments. The Office rejects claims 28-34, 37-40, 43-51, 54, and 56 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description. Claims 28-34, 37-40, 43-51, 54, and 56 also are rejected by the Office under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Reconsideration of these objections and rejections is hereby requested.

Discussion of Claim Objections

Claims 34, 37, 40, 51, and 54, and therefore claims dependent thereon (e.g., claim 56), have been amended to remove non-elected subject matter from the claims. Accordingly, the Office's objection to the claims as allegedly containing non-elected embodiments is believed to be moot.

Discussion of Rejections under Section 112, first paragraph

The Office has rejected the pending claims for allegedly lacking written description and enablement. These rejections are traversed for the following reasons.

A. Written Description Requirement

Regarding the written description rejection, the Office contends that the specification does not adequately describe a transgenic mouse whose genome comprises a DNA sequence encoding an expressible dominant negative protein to a Fos protein having a desired phenotype (see page 6 of the Office Action). The Office also contends that the specification does not provide a representative number of species of a transgenic mammal or animal containing a gene encoding an expressible dominant negative protein to a Fos protein (see page 6 of the Office Action). Additionally, the Office indicates that the state of the art of creating transgenic animals was unpredictable at the filing date of the application.

The specification describes multiple phenotypes associated with a dominant negative nucleic acid binding protein (e.g., Fos), such as decreased cell growth, suppression of neoplastic growth, decreased or inhibited foci and/or colony formation (see, e.g., pages 35-36, paragraph [0087]; page 37, paragraph [0090]; and pages 55-58, paragraphs [0138]-[0139]), in addition to the "skinny" phenotype described in Example 14 of the specification. Such phenotypes can be elicited by expression of the dominant negative nucleic acid binding protein (e.g., Fos) throughout the whole animal, or in specific tissues by way of a tissue-specific promoter. The specification describes numerous acceptable promoters, including tissue-specific promoters, at, for example, pages 33-34, paragraphs [0083]-[0084]. Additionally, the specification describes additional regulatory elements, such as enhancers (see, e.g., pages 36-37, paragraph [0089]; pages 32-33, paragraph [0081]; and pages 34-35, paragraph [0085]); expression vectors (see, e.g., pages 32-33, paragraph [0081]); construction of expression vectors (see, e.g., page 35, paragraph [0086]); introduction of the transgene into cells (see, e.g., pages 34-35, paragraph [0085]; and pages 37-40, paragraphs [0091]-[0096]); and animals to be targeted by the transgene (see, e.g., pages 32-33, paragraph [0081]; and pages 66-67, paragraph [00159]). Moreover, the specification provides numerous examples of specific constructs (e.g., for creation of transgenic animals) (see, e.g., page 52, paragraph [0130]; page 53, paragraph [0131]; and Figures 2, 6, and 23). Additionally, the specification provides screening methods to ascertain expression of the dominant negative nucleic acid protein (see, e.g., pages 35-36, paragraph [0087]-[0088]).

Given the extensive written description provided in the specification, one of ordinary skill in the art would have recognized that Applicants had possession of the claimed invention at the time the application was filed. Therefore, the written description rejection is improper and should be withdrawn.

B. Enablement Requirement

Regarding the enablement rejection, the Office contends that the state of the art of creating transgenic animals was unpredictable at the filing date of the application, such that the successful incorporation and expression of a transgene to create a desired phenotype was unpredictable. As support for the unpredictability, the Office cites to Moreadith et al. (*J. Mol. Med., 75,* 208-216 (1997)), which the Office indicates supports phenotypic unpredictability in knockout mice (see page 10 of the Office Action). The specification, however, is not directed to a method of creating a "knockout mouse" as described in Moreadith et al. Specifically, the specification does not describe the replacement of genomic sequences via homologous recombination (e.g., gene targeting) as described by Moreadith et al. but rather, the inhibition of binding of nucleic acid binding proteins by introduction of dominant negative nucleic acid proteins.

The Office contends that the level of expression and specificity of a transgene, as well as the resulting phenotype of the transgenic mouse, are directly dependent on the transgene construct (see page 10 of the Office Action). As described above, the specification adequately describes and enables the creation of a transgene construct by describing the individual components (e.g., promoters, enhancers, and other regulatory elements), expression vectors and the construction thereof, introduction of the transgene into cells, animals to be targeted by the transgene, specific transgene constructs, screening methods to ascertain transgene expression, and phenotypes associated with transgene expression. Specifically, the specification describes the successful creation of a transgenic mouse in Example 14, which transgenic mouse expresses the dominant negative 3heptadF C/EBP protein.

Moreover, Applicants have created numerous transgenic mouse models using the methods recited in the specification, as described in the accompanying 37 C.F.R. § 1.132 Declaration of Charles R. Vinson, Ph.D. The Rule 132 Declaration specifically reports on the creation of transgenic mice expressing a dominant negative, acidically modified Fos protein (A-FOS) under the control of the tetracycline operator region. Following a multi-stage skin carcinogenesis model, the expression of the A-FOS transgene in the transgenic mice effectively prevents the production of papillomas and carcinomas as was observed in control

littermates. Additionally, when papillomas were produced prior to A-FOS expression, progression to malignant carcinomas was prevented and a trans-differentiation into benign sebaceous adenomas was observed.

The Office contends that there is no evidence that indicates the expressible dominant negative 3heptadF C/EBP is an effective dominant negative protein to the Fos protein (see page 12 of the Office Action). However, Example 14 of the specification demonstrates that it is possible to produce a dominant negative nucleic acid binding protein that functions in accordance with the invention in an *in vivo* environment in an animal (see page 68, paragraph [0163]). The dominant negative 3heptadF C/EBP functions as a dominant negative to the non-mutant C/EBP protein (see pages 68-69, paragraph [0164]). The specification provides support for the creation of transgene constructs designed to function as a dominant negative to non-mutant Fos, for example, for the creation of a transgenic animal (see, e.g., page 36, paragraph [0088] of the specification; page 52, paragraph [0130]; page 53, paragraph [0131]; and Figures 2, 6, and 23). The constructs contain the CMV promoter to drive expression of the gene encoding the dominant negative 4heptadFos (i.e., a dominant negative Fos protein), or a tissue-specific promoter (see, e.g., pages 36-37, paragraphs [0088]-[0089] of the specification). Furthermore, as described above, the accompanying Rule 132 Declaration of Charles R. Vinson, Ph.D. reports on the successful creation of transgenic mice expressing a dominant negative, acidically modified Fos protein using the methods recited in the specification.

The Office contends that claims 28-34 and 37 encompass the introduction of an isolated DNA molecule encoding an acidically modified nucleic acid binding protein containing an N-terminal extension of acidic amino acid residues into *any* cell of the non-human animal. The Office specifically alleges that such claims are too broad to be supported by the specification. The claims have been amended to recited *embryonic* cell, which is supported by the specification at, for example, Example 13. The Office contends that embryonic stem (ES) cell technology is generally limited to the mouse system, and cites, e.g., Moreadith et al. as support for this contention. As discussed above, Moreadith et al. is directed to "knockout mouse" technology, in which a genomic fragment is replaced via homologous recombination, which is not indicative of the present invention. Moreover, the specification describes multiple routes of introducing the transgene into embryonic cells of the animal, including transfecting a retrovirus constructed to contain the DNA sequence encoding a dominant negative leucine-zipper containing protein (e.g., Fos) to provide a complete shuttle vector harboring the dominant negative nucleic acid sequence as a transgene and directly injecting a transgene into an embryo, in addition to the use of ES cell technology

(see pages 66-67, paragraph [0159]). Indeed, Example 14 describes the introduction of the transgene construct by injection of the construct into early-stage mouse embryos (see, e.g., pages 68-69, paragraph [0164]). Accordingly, the specification is enabling and adequately describes the creation of transgenic animals, including non-human mammals.

For the above reasons, the specification is considered to provide adequate written description and an enabling disclosure for a transgenic animal comprising a dominantly negative nucleic acid binding protein (e.g., Fos protein) and method of producing the same.

Conclusion

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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